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(54) ANTISEPTIC COMPOSITIONS

(71) We, STAFFORD-MILLER LIMITED, a British Company of 166, Great North Road, Hatfield, Hertfordshire, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to an antiseptic composition comprising urea peroxide, glycerol, and a carboxypolymethylene polymer or salt thereof.

Hydrogen peroxide is a well known antiseptic and has been extensively employed in aqueous solution for the treatment of infectious processes in both human and veterinary topical therapy. Hydrogen peroxide can be used *per se*, after suitable dilution, or it can be derived from solid compounds which form salts or additive compounds with hydrogen peroxide; such as sodium perborate, sodium carbonate peroxide, sodium peroxyphosphate, urea peroxide and potassium persulfate. When added to water, these compounds hydrolyze into hydrogen peroxide and the corresponding carrying salt.

Although extensively employed for treating all parts of the body, hydrogen peroxide has proved especially valuable for treating the mucous membranes of the oral cavity. Partly as a consequence of oxygen tissue metabolic and reparative requirements (by a mechanism which is not clearly understood), partly as a consequence of its broad antibacterial effects against gram positive and gram negative cocci, bacilli and spirochetal forms as well as many varieties of yeasts and fungi, and partly because of its cleaning and haemostatic effects, hydrogen peroxide is extensively recommended and used for the treatment of bacterial and viral infections and for tissue inflammations of non-microorganic origin.

The principal limitation of the commonly used peroxide aqueous solutions, however, is their brief period of contact and function on oral tissues. Since many oral bacteria, as well as saliva, contain high concentrations of the enzyme catalase and other peroxidases, the hydrogen peroxide is rapidly decomposed into gaseous oxygen and water. It is a well known fact that the antibacterial effects of peroxides are exercised only at the instant that the peroxide decomposes to release nascent oxygen. The gaseous oxygen molecules subsequently formed by combination of the nascent oxygen atoms have no antibacterial effects or tissue oxygenating potential. Thus, there is only transitory contact of the active oxygenating agent with the affected tissues. Furthermore, the low viscosities of water solutions of hydrogen peroxide itself and the water solutions of hydrogen peroxide - additive salts, do not allow the active material to stay in contact with affected tissues for as long as is desirable because of the constant flushing effects of salivary secretions. This tendency toward rapid decomposition of hydrogen peroxide into gaseous oxygen and water and the rapid removal of peroxide solutions has severely limited their application to, and utility on, oral tissues.

It would be highly desirable, therefore, to extend the period of oxygen release from hydrogen peroxide for considerably longer periods, as well as to increase the period of retention on the tissues.

It is, therefore, an object of the present invention to provide an antiseptic composition useful, *inter alia*, for the treatment of oral soft tissue inflammation, which is capable of being retained on oral tissue for extended periods of time and which also exhibits sustained or prolonged release of nascent oxygen.

The antiseptic composition of the invention comprises urea peroxide as a source of hydrogen peroxide in a slowly dispersing solvent made of glycerol which is thickened with a glycerol-soluble polymer. The objectives of imparting high viscosity characteristics to the glycerol carrier of the invention, and of achieving prolonged release

[1

of nascent oxygen, are obtained by the use of a carboxypolymethylene polymer, and preferably by the use of the glycerol-soluble neutralized alkali metal or amine salts of such a polymer.

Carboxypolymethylene polymers are effective agents for thickening glycerol (for instance, see Cohen, pages 42 et seq., "Soap and Chemical Specialties" November 1956). In accordance with the present invention, however, it has been found that, not only do carboxypolymethylene polymers serve as effective thickening agents for solutions of urea peroxide in glycerol but, surprisingly, these polymers impart sustained nascent oxygen release effects to such solutions and, moreover, impart greater tissue adherence characteristics thereto.

The carboxypolymethylene polymers useful in the compositions of the present invention are well known, typical examples being disclosed, for example, in U.S. Patents Nos. 2,798,053; 2,858,218; 2,923,692; and 2,985,625. Preferably, the carboxypolymethylene polymers used in the compositions of the invention are of the type described in United States Patent No. 2,798,053, and comprise interpolymers of a major proportion of one or more alpha, beta-olefinically unsaturated carboxylic acids, and a minor proportion of a polyalkenyl polyether of a polyol, suitably a polyallyl ether of a polyhydric alcohol containing at least three hydroxyl groups.

Examples of alpha, beta-olefinically unsaturated carboxylic acids described in United States Patent No. 2,798,053, and which may be employed to produce carboxypolymethylene polymers which may be used in the composition of the invention, are acrylic acid, methacrylic acid, maleic acid and maleic anhydride. Examples of suitable polyallyl polyethers of polyols include the allyl ethers having an average of at least two allyl groups per molecule and which are ethers of sucrose, sorbitol, glucose, mannitol, pentaerythritol, 1,2,3-butanetriol and xylitol. Additional monomers may be included in the polymer, if desired. Such other monomers include vinyl acetate, acrylamide and vinyl pyrrolidone.

Carboxypolymethylene polymers which are suitable for use in the antiseptic compositions of the invention are commercially available under the trade name "Carbopol" (the word "Carbopol" is a Registered Trade Mark).

The preferred antiseptic compositions of this invention comprise urea peroxide, glycerol and a carboxypolymethylene polymer or salt thereof, the latter being incorporated in the formulation in an amount sufficient to provide a gel having a viscosity of at least 1000 centipoises at 25°C.

The glycerol used in the compositions is preferably anhydrous in order to impart maximum chemical stability to the active urea peroxide agent. However, water may also be present in an amount of up to 10% of the composition if it is desired, for example, to incorporate auxiliary agents in the composition which may have only a limited solubility in glycerol but greater solubility in water. Whenever water is so utilized in the compositions it is desirable, though not essential, to also incorporate a peroxide stabilizing agent. Such agents, and their mode of use are known. Examples of peroxide stabilizers include phenacetin, acetanilide, 8-hydroxyquinoline, stannous salts and ethylenediaminetetracetic acid derivatives.

The preferred carboxypolymethylene polymers for use in the compositions of the invention are copolymers of from 97.5 to 99.8, preferably about 99, percent by weight of acrylic acid and from 0.2 to 2.5, preferably about 1, percent by weight of polyallyl sucrose having at least two, preferably about 5.8, allyl groups per sucrose molecule. Desirably, such polymers are employed as the neutral salts thereof. By "neutral" is meant that the pH of a 1 weight percent water solution of the salt of the polymer has a pH of from 5 to 9, and preferably from 6 to 8.

Glycerol-soluble neutralizing agents which can be employed to form the salts of the carboxypolymethylene polymers include the various alkanolamines such as monoethanolamine, diethanolamine, triethanolamine and triisopropanolamine; alkali metal hydroxides such as sodium hydroxide and potassium hydroxide; pyridine and other amines and other glycerol-soluble alkaline agents. The use of the ethanolamines is preferred.

It is possible to add to the antiseptic compositions of the invention, if desired, other glycerol-soluble components intended to serve various functions. Peroxide stabilizers, such as 8-hydroxyquinoline, can, as noted above, also be added. Ethanol or water may serve as part of the composition, if desired, as co-solvents for other compounds. Therapeutically acceptable dyes and/or flavouring agents can also be added to the formulation. In fact, any agent which is soluble in glycerol or in glycerol mixtures as described, is non-toxic at the levels used, does not detract from the homogeneity or optical clarity of the finished product, and which does not reduce the inherently high stability of the urea peroxide in glycerol, can be incorporated, if desired.

The proportions of the components of the composition of the invention can be varied within relatively wide limits. In general, the urea peroxide is used in therapeutically effective proportions, such as from 3 weight percent to 25 weight percent, based on the weight of the antiseptic composition. Levels below the lower limit specified will tend

to release insufficient oxygen to achieve the desired therapeutic effect, while those concentrations above the upper limit specified begin to be incompletely soluble in the glycerol used as a carrier, and may be irritating to the oral tissue of a user.

The concentrations of the neutralized carboxypolymethylene polymer may also be varied in order that the finished composition ranges in viscosity from a thickened syrup-like liquid of about 1,000 centipoises at room temperature (25°C.) to extremely stiff gels with viscosities of 500,000 or more centipoises at room temperature. The specific amounts of polymer to be employed in order to achieve the desired viscosity depends, in part, upon factors such as the exact nature of the polymer and the presence or absence of other co-solvents in the glycerol composition. In general, however, amounts of from 0.05 to 5, preferably from 0.1 to 2, and more preferably from 0.4 to 1.5, weight percent (based on the total weight of the antiseptic compositions) of polymer are employed.

The antiseptic compositions of the invention are preferably formulated by first thoroughly dispensing the carboxypolymethylene polymer into the glycerol and thereafter dissolving the urea peroxide and any further ingredients in the thickened solution, a clear homogeneous gel resulting. Thus, the powdered polymer may be slowly added to the glycerol while agitating the mixture with a stirrer. When the polymer is employed as the neutralized salt thereof, it is preferred to add the neutralizing agent to the mixture after the polymer has been dispersed and dissolved in the glycerol, and subsequent to the addition of the urea peroxide and other adjuvants.

In order that the invention may be well understood the following Examples of compositions according to the invention are given by way of illustration only. In the Examples all parts and percentages are given by weight:

EXAMPLE 1

Urea Peroxide	8.00%
Anhydrous Glycerol	85.30%
Carboxypolymethylene polymer*	1.00%
Triethanolamine	0.60%
Ethanol	5.00%
Oil of Peppermint	0.10%

*"Carbopol 934"—a copolymer of 99 percent acrylic acid 1 percent polyallyl sucrose having an average of about 5.8 allyl groups per sucrose molecule.

The polymer is dispersed with high speed stirring in the glycerol under an atmosphere of reduced pressure. When dissolved, the urea peroxide, ethanol, and oil of peppermint are dissolved in slightly thickened solution. Finally, the triethanolamine is incorporated with stirring, thus further thickening the composition. The resulting product is a clear, homogeneous, viscous gel. The composition is eminently satisfactory for the therapy of minor gingival inflammations and for the antiseptic treatment of oral soft tissue infections.

EXAMPLE 2

Urea Peroxide	11.00%
Carboxypolymethylene polymer*	0.60%
Phenacetin	0.05%
Mixed Flavour	0.05%
Triethanolamine	0.40%
Anhydrous Glycerol	87.90%

*"Carbopol 940"—a copolymer of acrylic acid and polyallyl sucrose having an average of about 5.8 allyl groups per sucrose molecule.

The preparation is made in the same manner as detailed for Example 1 to form a clear, homogeneous, viscous gel suitable for the treatment of oral infections.

The more prolonged oxygen release rates achieved by use of the compositions of this invention as compared with those obtained employing simple solutions of urea peroxide in glycerol, have been demonstrated by both *in vitro* and *in vivo* techniques, as described below:

In Vitro Tests

The oxygen-release characteristics of the compositions described in Example 2 were compared with those of a simple solution of 11 percent urea peroxide in anhydrous glycerol by a technique wherein either 25 ml. of a .002% solution of lyophilized catalase or 25 ml. of pooled human saliva was placed in a graduated cylinder. Exactly 0.3 cc of the sample being studied was added and the graduated cylinder immediately capped with an inverted 10 ml. microburet. A soap film was created inside the buret, set at the zero mark, and observed to indicate the volume of oxygen liberated. A stop watch was started simultaneously with the addition of the sample, and the gas volume recorded at one minute intervals. The determinations using catalase solution were carried out until there was no further gas evolved, while those using saliva were terminated after approximately half the expected gas had evolved. Table 1 shows the volume of oxygen liberated by catalase with the composition of Example 2 and by the simple solution of 11 percent urea peroxide in glycerol.

TABLE I

cc of Oxygen Liberated By In Vitro Catalase Treatment

Time (Minutes)	Example 2 Composition	Urea Peroxide-Glycerol
0	0.00	0.00
5	2.63	4.20
10	3.82	—
15	4.38	—
20	4.62	—

It can be seen that the composition of Example 2 produced oxygen continuously for a 20 minute period while the simple solution of urea peroxide in anhydrous glycerol had lost all of its oxygen at the end of 5 minutes. The prolonged oxygen release exhibited by the composition of Example 2 indicates the utility of such a composition in inducing extended therapeutic effects on oral soft tissue.

Table II indicates the results of a similar study, in which human saliva rather than the catalase solution was utilized to release oxygen from the above test formulation.

TABLE II

cc of Oxygen Liberated By In Vitro Saliva Treatment

Time (Minutes)	Example 2 Composition	Urea Peroxide-Glycerol
0	0.00	0.00
10	0.05	0.06
20	0.20	1.80
30	0.45	2.13
40	0.70	—
50	1.00	—
60	1.35	—
70	1.70	—
80	2.00	—

Again it will be noted that the composition of Example 2 continued releasing oxygen for periods considerably longer than the oxygen-release time period observed for the urea peroxide in glycerol.

In Vivo Tests

An *in situ* investigation has also been conducted to study the combined adherence to human oral tissue and oxygen release characteristics of the antiseptic compositions of this invention. Five volunteer subjects had a premeasured amount of the composition described in Example 2 applied to the oral mucosa on their mandibular gingiva in the area of the first bicuspid tooth. Exactly one minute later the area of application was carefully wiped with a cotton swab to remove as much as possible of the originally applied product, still present as a residue. The entire cotton swab was then dropped into a test tube containing dilute, acidified potassium permanganate decolourisation of which indicated that some applied product was still present and that it still had a measurable quantity of available oxygen present. After the procedure had been completed, it was repeated at a later time except that the area of application was not swabbed until two minutes after application has elapsed. At a later time, the procedures were repeated after 3 minutes, and then after 4 minutes, and so on, until the time period was reached when the swab no longer decolourized the permanganate.

In a like manner, an additional five subjects were subjected to a similar test in which, in lieu of the composition of Example 2 hereof, a simple solution of 11 percent urea peroxide in anhydrous glycerol was applied to their gingivae. The procedure outlined above was repeated until a time period was reached at which the swab no longer decolourized the permanganate reagent.

The five subjects in each group were then reversed and subjected to treatment with the product not previously employed. At the conclusion of the study each subject had been identically treated with each product. Table III shows the duration of tissue adherence and continuing oxygen release for each subject with the composition of Example 2 and with the solution of urea peroxide in glycerin. A "plus" reading at 1 minute but not at 2 minutes is recorded as "1.5" in the Table; that at 4 minutes but not at 5 minutes is recorded as "4.5", etc.:

TABLE III

Persistence of Oxygenating Effects on Oral Tissue

Subject	Duration of Effect in Minutes: Example 2	Urea Peroxide-Glycerol
1	5.5	1.5
2	5.5	0.5
3	5.5	1.5
4	7.5	1.5
5	3.5	1.5
6	4.5	1.5
7	5.5	2.5
8	4.5	0.5
9	6.5	3.5
10	6.5	3.5
Average	5.5	1.8

It may be noted that the average duration of effective oxygen action at the site of application on human oral mucous mem-

branes was more than three times as long, and that each participant in this controlled study demonstrated considerably longer retention, for the composition of Example 2 as compared with the simple solution of urea peroxide in anhydrous glycerol. Similar effects can be expected when the respective products are used for therapeutic purposes.

WHAT WE CLAIM IS:—

1. An antiseptic composition comprising urea peroxide, glycerol, and a carboxypolymethylene polymer or glycerol-soluble metal or amine salt thereof.

2. A composition as claimed in claim 1 in which the carboxypolymethylene polymer or salt thereof is present in an amount sufficient to impart to said antiseptic composition a viscosity of at least 1000 centipoises at 25°C.

3. An antiseptic composition as claimed in claim 1 or claim 2 comprising a clear, homogeneous gel containing from 3 to 25 percent by weight of urea peroxide and from 0.05 to 5 percent by weight of the carboxypolymethylene polymer or neutral salt thereof.

4. An antiseptic composition as claimed in any one of the preceding claims in which the carboxypolymethylene polymer is employed in the form of a neutral ethanolamine salt.

5. An antiseptic composition as claimed in any one of the preceding claims in which the carboxypolymethylene polymer is an interpolymer of a major proportion of an alpha, beta-olefinically unsaturated carboxylic acid and a minor proportion of a polyalkenyl polyether of a polyol.

6. An antiseptic composition as claimed in claim 5, in which the interpolymer is a copolymer of (a) acrylic acid, methacrylic acid, maleic anhydride, or maleic acid and (b) a polyallyl polyether of a polyol having at least three hydroxyl groups, said polyether having an average of at least two allyl groups per molecule of polyol.

7. An antiseptic composition as claimed in claim 6 in which said interpolymer is a copolymer of from 97.5 to 99.8 percent by weight of acrylic acid and from 0.2 to 2.5 percent by weight of polyallyl sucrose having at least two allyl groups per sucrose molecule.

8. An antiseptic composition as claimed in claim 7, in which the copolymer is a copolymer of about 99 weight percent acrylic acid and about 1 weight percent polyallyl sucrose having an average of about 5.8 allyl groups per sucrose molecule.

9. An antiseptic composition as claimed in claim 1 substantially as hereinbefore described with reference to the Examples.

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